45. The method of Claim 33, wherein the subject is suffering from hepatic cirrhosis.--

SUPPORT FOR THE AMENDMENTS

Newly-added Claims 30-45 are supported by the specification at pages 4-60 and the original claims. No new matter is believed to have been added to this application by these amendments.

REMARKS

Claims 30-45 are now pending. Favorable reconsideration is respectfully requested.

The present invention is based, in part, on the discovery that a relationship exists between (1) the redox status of the intracellular glutathione level in macrophages and (2) the production of IL-6, IL-12, and NO in the macrophages.

The inventors have discovered that reducing the level of reductive glutathione in macrophages (a) increases the capability of the macrophages to produce IL-6 and (b) reduces the capability of the macrophages to produce IL-12 and NO. The reduction in the level of reductive glutathione induces a Th2 response and suppresses the cellular immune response.

The significance of this finding is described in the present specification (see, for example, Figures 1 and 2) and the publication Murata et al., International Immunology, Vol. 14, No. 6, pp. 627-636, submitted herewith for the Examiner's review. See especially page 628, column 2, and page 631, second column, under "Conversion of RMp to OMp and a prophylactic intervention," and page 633, second column. See also Murata et al., International Immunology, Vol. 14, No. 2, pp. 201-212, submitted herewith

Thus, the present invention relates to a method of inducing a Th2 response in a subject, comprising reducing the content of reductive glutathione in macrophages in the subject, thereby (a) increasing the capability of the macrophages to produce IL-6 and (b) decreasing the capability of the macrophages to produce IL-12 and NO. See Claim 30.

The present invention also relates to a method of suppressing cellular immune responses in a subject by skewing the Th1/Th2 balance in macrophages to Th2, comprising reducing the content of reductive glutathione in the macrophages in the subject. See Claim 31.

The rejection of Claims 1-3, 11, and 20-29 under 35 U.S.C. §112, first paragraph, is believed to be moot in view of the cancellation of these claims. In addition, the newly-added claims are clearly enabled by the specification.

The Examples of the present application demonstrate the relationship between the Th1/Th2 balance and cellular reductive glutathione content and cytokine production. As described at page 14, lines 11-13, one skilled in the art can readily monitor the level of reductive glutathione in macrophages as described in the specification (see, for example, Example 3 at page 25) and correct an abnormal Th1/Th2 balance. Foe example, an patient with gastrointestinal inflammatory disease (IBD) with an increased content of reductive glutathione in macrophages, above 2 nmole/10^5 cells, may be treated according to the present invention to reduce that amount to 0.5 nmole/10^5 cells. See also page 31, lines 11-15: when homeostasis of immunity is in a state of imbalance, such disease occurs and the method of the present invention may be used. In addition, the data presented in the specification at, for example, Example 9, Table 1, Example 10, Table 2, Example 13, demonstrate the effectiveness of the present invention.

Usually, IBD, chronic rheumatoid arthritis, hepatitis, and hepatic cirrhosis are considered to be treatable by suppressing cellular immunity. The Inventors have discovered that suitable treatment differs depending on the disease stage. More particularly, for IBD-type disease, as discussed in Murata et al. attached hereto, "infiltration of inflammatory cells in inflamed sites may ne triggered initially by OMp (oxidative macrophage) resulting in the release of anti-inflammatory cytokines, which in turn may trigger the conversion of OMp to Rmp (reductive macrophage). Subsequent tissue injury is ascribed to RMp." See page 633, second column, lines 9-15 from the bottom.

That is, the treatment of increasing RMp (enhancing cellular immunity) is good for prevention of infiltration (or aggregation) of inflammatory cells; meanwhile, decreasing Rmp (suppressing cellular immunity) is good for preventing tissue injury caused by inflammatory cytokines. Premeasurement of GSH levels in macrophages, which can be accomplished without undue experimentation by one skilled in the art, can be used to determine whether treatment would be suitable.

Based on the foregoing, the claimed methods are enabled by the specification. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The rejection of Claims 1-3, 11, and 20-29 under 35 U.S.C. §112, second paragraph, is believed to be moot in view of the cancellation of these claims. The newly-added claims are believed to address the issues raised in the Official Action. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Applicants submit that the application is in condition for allowance. Early notice of such action is earnestly solicited.

Respectfully submitted,

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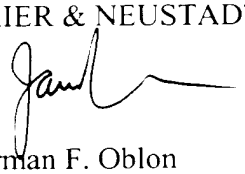

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Serial No.: 09/731,830
Amendment Filed On: November 23, 2001

IN THE CLAIMS

--Claims 1-3, 11, and 20-29 (Cancelled)

Claims 30-45 (New)--.